· SEQUENCE LISTING

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Hochkenpel, Heinz-Kurt

Garcia-Echeverria, Carlos

Furet, Paacal

<120> Inhibitors of the Interaction of P53 and MDM2

<130> 4-20937/A/PCT

<140> herewith

<141> 1999-01-05

<150> PCT/EP97/03549

<151> 1997-07-04

<160> 83

<170> PatentIn Ver. 2.0

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<220>
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Xaa Xaa Phe Xaa Xaa Xaa Trp Xaa Xaa Xaa
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     <220>
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     <220>
     <221> VARIANT
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<223> X= arginine, histidine, glutamic acid, cysteine,

<213> Artificial Sequence

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[-1
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serine or preferably aspartic acid.

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Met Pro Arg Phe Met Asp Tyr Trp Gln Gly Leu Asn Arg Gln Ile Lys
                                                           15
                                      10
  1
                   5
```

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Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
                                      25
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     <221> VARIANT
     <222> (4)
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<223> X = histidine, phenylalanine, or preferably
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<222> (6)
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<400> 10
Phe Xaa Xaa Xaa Trp Xaa Xaa Xaa
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Xaa Phe Xaa Xaa Xaa Trp Xaa Xaa Xaa
                   5
  1
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<210> 12
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Pro Ala Phe Thr His Tyr Trp Pro
5
      1
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                       5
      1
     <210> 14
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                      5
1
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      1
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      1
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                      5
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<220>
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      1
                      5
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    <400> 20
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     1
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    <221> VARIANT
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<222> (8)
    <223> X = Pro-NH2
    <400> 21
    Xaa Ala Phe Thr His Tyr Trp Xaa
      1
    <210> 22
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. C = = = = = =
    <223> Description of Artificial Sequence:peptide
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    <222> (1)
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     <221> VARIANT
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     <223> X = Pro-NH2
     <400> 22
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Xaa Thr Phe Ser Asp Tyr Trp Xaa
                       5
    <210> 23
    <211> 8
    <212> PRT
    <213> Artificial Sequence
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    <221> VARIANT
    <222> (1)
I I I I I I I I
    <223> X = Ac-Pro
    <220>
    <221> VARIANT
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    <223> X = Pro-NH2
    <400> 23
    Xaa Arg Phe Met Asp Tyr Trp Xaa
     1
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<210> 24
    <211> 12
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    <221> VARIANT
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    <223> X = Pro-NH2
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                       5
                                          10
      1
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    <223> Ac-Gln
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<221> VARIANT
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    Xaa Pro Thr Phe Ser Asp Leu Trp Lys Leu Leu Xaa
      1
                                         10
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    <222> (1)
    <223> X = Ac-Gln
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    <222> (12)
    <223> X = Pro-NH2
<400> 26
    Xaa Glu Thr Phe Ser Asp Tyr Trp Lys Leu Leu Xaa
                        5
                                            10
       1
. T. T. C. C. T.
    <210> 27
    <211> 12
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     <222> (1)
     <223> X = Ac-Val
```

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<220>
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    <223> X=Phe-NH2
    <400> 27
    Xaa Gln Asn Phe Ile Asp Tyr Trp Thr Gln Gln Xaa
                                         10
                      5
      1
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    <223> X = Ac-Ile
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    <400> 28
    Xaa Asp Arg Ala Pro Thr Phe Arg Asp His Trp Phe Ala Leu Glx
                                                              15
                                          10
     1
                      5
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     <400> 29
    Xaa Arg Pro Ala Leu Val Phe Ala Asp Tyr Trp Glu Thr Leu Xaa
```

```
15
                                         10
      1
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    <222> (1)
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    <220>
    <221> VARIANT
    <222> (15)
    <223> X = His-NH2
    <400> 30
    Xaa Ala Phe Ser Arg Phe Trp Ser Asp Leu Ser Ala Gly Ala Xaa
      ĺ
                                                              15
                      5
                                         10
    <210> 31
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    <400> 31
    Thr Gly Pro Ala Phe Thr His Tyr Trp Ala Thr Xaa
. 1
                                          10
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    <400> 32
    Met Pro Arg Phe Met Asp Tyr Trp Glu Gly Leu Xaa
                                        10
      1
    <210> 33
    <211> 14
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T.
    <220>
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    <222> (1)
    <223> X = Ac-Cys(Acrld) or Ac-Cys
    <220>
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    <222> (14)
    <223> X = Pro-NH2
     <400> 33
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```
Xaa Gly Gln Pro Thr Phe Ser Asp Tyr Trp Lys Leu Leu Xaa
                                         10
                      5
      1
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    <223> X = Pro-NH2
    <220>
    <221> UNSURE
    <222> (1)
    <223> X = Ac-Cys
    <400> 34
    Xaa Gly Gln Pro Thr Phe Ser Asp Tyr Trp Lys Leu Leu Xaa
                                          10
                       5
     1
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    Xaa Gly Pro Thr Phe Ser Asp Leu Trp Xaa
                                         10
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    <223> X = Ac-Cys
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    <222> (10)
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Xaa Gly Pro Thr Phe Ser Asp Leu Trp Xaa
                                         10
      1
    <210> 37
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     <223> Description of Artificial Sequence:peptide
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    <223> X = Ac=Cys(Acrd)
    <220>
    <221> VARIANT
    <222> (9)
    <223> X = Pro-NH2
    <400> 37
    Xaa Pro Thr Phe Ser Asp Leu Trp Xaa
                        5
      1
ten that the ten ten ten
    <210> 38
    <211> 9
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    <213> Artificial Sequence
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    <220>
    <221> VARIANT
    <222> (1)
    <223> x = Ac-Cys
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    <221> VARIANT
    <222> (9)
    <223> X = Pro-NH2
    <400> 38
    Xaa Pro Thr Phe Ser Asp Leu Trp Xaa
                       5
    <210> 39
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    <220>
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    <220>
    <221> VARIANT
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```
<223> X = Pro-NH2
    <400> 39
    Xaa Gly Ser Gly Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Xaa
                                                             15
                                         10
                      5
      1
    <210> 40
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N
T
    <221> VARIANT
ű
    <222> (1)
     <223> X = Biotin-Ser
     <220>
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     <222> (16)
     <223> X = Pro-NH2
     <400> 40
     Xaa Gly Ser Gly Gln Pro Thr Phe Ser Asp Leu Trp Lys Leu Leu Xaa
```

```
15
                                            10
      1
                       5
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OSEILIVI I SEESS
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     <221> VARIANT
     <222> (16)
     <223> X = Pro-NH2
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     Xaa Gly Ser Gly Gln Glu Thr Phe Ser Asp Tyr Trp Lys Leu Leu Xaa
                                                                  15
                                            10
       1
                        5
    <210> 42
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    <223> X = Lys-NH2
    <400> 42
    Xaa Met Pro Arg Phe Met Asp Tyr Trp Glu Gly Leu Asn Arg Gln Ile
                                         10
                                                             15
                      5
      1
    Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Xaa
                                     25
                 20
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                                                             15
                                         10
                      5
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    <221> VARIANT
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    <220>
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    <222> (30)
    <223> product = bAla
    <220>
    <221> VARIANT
    <222> (31)
DGEL4371.CZE59
    <223> X = Lys(Biotin)-NH2
    <400> 44
    Xaa Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
                                           10
                                                                15
     1
    Ala Met Pro Arg Phe Met Asp Tŷr Trp Glu Gly Leu Asn Ala Xaa
                                                            30
                                       25
                  20
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<400> 45
    Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
                                                              15
                                          10
                      5
      1
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     <400> 46
     Xaa Thr Phe Ser Asp Tyr Trp Xaa
      1
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<210> 47
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    <221> VARIANT
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    <400> 47
    Xaa Thr Phe Ser Asp Tyr Trp Xaa
      1
                      5
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     <221> VARIANT
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     <400> 48
     Xaa Ala Phe Thr His Tyr Trp Xaa
     . 1
Ф
                       5
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     <220>
     <221> VARIANT
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     <400> 49
     Xaa Ala Phe Thr His Tyr Trp Xaa
     . 1
li sessi
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     <211> 8
     <212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:peptide
     <220>
     <221> VARIANT
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<222> (1)
    <223> x = Ac-Cys
    <220>
    <221> VARIANT
    <222> (8)
    <223> X = Cys-NH2
     <400> 50
    Xaa Arg Phe Met Asp Tyr Trp Xaa
1
     <210> 51
     <211> 8
<212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:peptide
     <220>
     <221> VARIANT
     <222> (1)
     <223> X = Ac-Cys
     <220>
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<221> VARIANT
    <222> (8)
     <223> X = Cys-NH2
     <400> 51
    Xaa Arg Phe Met Asp Tyr Trp Xaa
      1
     <210> 52
<211> 8
     <212> PRT
     <213> Artificial Sequence
     <220>
<223> Description of Artificial Sequence:peptide
     <220>
     <221> VARIANT
     <222> (1)
     <223> X = Ac-Glu
     <220>
     <221> VARIANT
     <222> (8)
     <223> X = Lys-NH2
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<400> 52
    Xaa Thr Phe Ser Asp Tyr Trp Xaa
                       5
      1
     <210> 53
     <211> 8
     <212> PRT ·
     <213> Artificial Sequence
     <220>
<223> Description of Artificial Sequence:peptide
     <220>
     <221> VARIANT
HTEET
     <222> (1)
     <223> X = CO-NH bridge (lactam peptide derivative)
     <220>
     <221> VARIANT
     <222> (1)
    ' <223> X = Ac-Glu
     <220>
     <221> VARIANT
     <222> (8)
     <223> X = CO-NH bridge (lactam peptide derivative)
```

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<220>
     <221> VARIANT
     <222> (8)
     <223> X = Lys-NH2
     <400> 53
     Xaa Arg Phe Met Asp Tyr Trp Xaa
      1
                      5
<210> 54
     <211> 8
     <212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:peptide
     <220>
     <221> VARIANT
     <222> (1)
     <223> X = Ac-Phe
     <220>
     <221> VARIANT
      <222> (3)
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<223> Product = Aib
<220>
<221> VARIANT
<222> (6)
<223> Product = Aib
<220>
<221> VARIANT
<222> (8)
<223> X = Leu-NH2
<400> 54
Xaa Met Xaa Tyr Trp Xaa Gly Xaa
 1
<210> 55
<211> 9
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:peptide
<220>
<221> VARIANT
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<222> (1) <223> X = Ac-Arg<220> <221> VARIANT <222> (4) <223> Product = Aib <220> <221> VARIANT <222> (7) <223> Product = Aib <220> <221> VARIANT <222> (9) <223> X = Leu-NH2<400> 55 Xaa Phe Met Xaa Tyr Trp Xaa Gly Xaa . . 1 <210> 56 <211> 9 <212> PRT <213> Artificial Sequence

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<220>
    <223> Description of Artificial Sequence:peptide
     <220>
     <221> VARIANT
     <222> (1)
     <223> x = Ac-Arg
     <220>
<221> VARIANT
     <222> (4)
     <223> Product = Aib
     <220>
<221> VARIANT
     <222> (8)
     <223> X = Ac3c
     <220>
     <221> VARIANT
     <222> (9)
      <223> X = Leu-NH2
      <400> 56
     Xaa Phe Met Xaa Tyr Trp Glu Xaa Xaa
       1
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<210> 57
    <211> 8
    <212> PRT
    <213> Artificial Sequence
    <220>
    <223> Description of Artificial Sequence:peptide
    <220>
     <221> VARIANT
     <222> (1)
     <223> X = Ac-Phe
. I I I II II II II
     <220>
     <221> VARIANT
     <222> (3)
     <223> Product = Aib
     <220>
     <221> VARIANT
     <222> (6)
     <223> Product = Aib
     <220>
     <221> VARIANT
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```
<222> (7)
     <223> X = Ac3c
     <220>
     <221> VARIANT
     <222> (8)
     <223> X = Leu-NH2
     <400> 57
     Xaa Met Xaa Tyr Trp Xaa Xaa Xaa
        1
<210> 58
      <211> 8
. I'I ''I ''I I'I I'I I'I
      <212> PRT
      <213> Artificial Sequence ...
      <220>
      <223> Description of Artificial Sequence:peptide
      <220>
      <221> VARIANT
      <222> (1)
      \langle 223 \rangle X = Ac-Phe
      <220>
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osaukaya caso
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<221> VARIANT
<222> (3)
<223> Product = Aib
<220>
<221> VARIANT
<222> (7)
<223> x = Ac3c
<220>
<221> VARIANT
<222> (8)
\langle 223 \rangle x = Leu-NH2
<400> 58
Xaa Met Xaa Tyr Trp Gln Xaa Xaa
 1
<210> 59
<211> 9
<212> PRT
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:peptide
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```
<220>
<221> VARIANT
<222> (1)
<223> x = Ac-Arg
<220>
<221> VARIANT
<222> (9)
<223> X = Leu-NH2
<400> 59
Xaa Phe Met Asp Tyr Trp Glu Gly Xaa
  1
<210> 60
<211> 8
<212> PRT
<213> Artificial Sequence
 <220>
<223> Description of Artificial Sequence:peptide
 <220>
 <221> VARIANT
 <222> (1)
 <223> x = Ac-Phe
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<220>
<221> VARIANT
<222> (8)
<223> x = Leu-NH2
<400> 60
Xaa Met Asp Tyr Trp Glu Gly Xaa
. 1
                  5
<210> 61
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:peptide
<220>
 <221> VARIANT
 <222> (1)
 <223> x = Ac-Phe
 <220>
 <221> VARIANT
 <222> (3)
```

```
<223> product = Aib
<220>
<221> VARIANT
<222> (8)
<223> x = Leu-NH2
<400> 61
Xaa Met Xaa Tyr Trp Glu Gly Xaa
                  5
 1
<210> 62
<211> 8
<212> PRT
<213> Artificial Sequence
<220>
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<220>
<221> VARIANT
 <222> (1)
 <223> x = Ac-Phe
 <220>
 <221> VARIANT
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<222> (6)
<223> Product = Aib
<220>
<221> VARIANT
<222> (8)
<223> X = Leu-NH2
<400> 62
Xaa Met Asp Tyr Trp Xaa Gly Xaa
                  5
 1
<210> 63
<211> 12
<212> PRT
<213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:peptide
 <400> 63
 Val Gln Asn Phe Ile Asp Tyr Trp Thr Gln Gln Phe
                   5
                                      10
  1
 <210> 64
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<211> 12
     <212> PRT
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:peptide
     <400> 64
     Thr Gly Pro Ala Phe Thr His Tyr Trp Ala Thr Phe
                                             10
                        5
       1
<210> 65
      <211> 14
      <212> PRT
" II II II II II II
      <213> Artificial Sequence
      <220>
      <223> Description of Artificial Sequence:peptide
      <400> 65
      Ile Asp Arg Ala Pro Thr Phe Arg Asp His Trp Phe Ala Leu
                                             10
                         5
       1
      <210> 66
       <211> 15
```

```
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:peptide
<400> 66
Pro Ala Phe Ser Arg Phe Trp Ser Asp Leu Ser Ala Gly Ala His
. 1
                                                          15
                                      10
                  5
<210> 67
<211> 30
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:primer DNA
 <400> 67
                                                                    30
 gcggatccga tggtgaggag caggcaaatg
 <210> 68
 <211> 33
 <212> DNA
 <213> Artificial Sequence
```

<220>

```
<223> Description of Artificial Sequence:primer DNA
<400> 68
                                                                   33
gcctgcagcc taattcgatg gcgtccctgt aga
<210> 69
<211> 32
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:primer DNA
<400> 69
                                                                    32
gcctgcagct aggggaaata agttagcaca at
<210> 70
 <211> 32
 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence:primer DNA
 <400> 70
                                                                    32
 gcctgcagct aatcttcttc aaatgaatct gt
```

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EN EN EN A IN THE STATE
    <u>L</u>
```

```
<210> 71
    <211> 27
    <212> DNA
    <213> Artificial Sequence
    <220>
    <223> Description of Artificial Sequence:primer DNA
    <400> 71
                                                                       27
    ggggatcctg aaatttcctt agctgac
     <210> 72
     <211> 29
     <212> DNA
<213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:primer DNA
     <400> 72
                                                                        29
     gcggatccat ggtgaggagc aggcaaatg
     <210> 73
     <211> 22
     <212> PRT
      <213> Artificial Sequence
```

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<220>
<223> Description of Artificial Sequence:peptide
<220>
<221> VARIANT
<222> (1)
<223> X = Biotin-Ser
<400> 73
Xaa Gly Ser Gly Glu Pro Pro Leu Ser Gln Glu Thr Phe Ser Asp Leu
                                                          15
                                      10
                  5
 1
Trp Lys Leu Leu Pro Glu
             20
<210> 74
<211> 18
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:peptide
 <400> 74
 Pro Pro Leu Ser Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
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10

5

1

<400> 76

15

57

58

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Glu Asn
     <210> 75
     <211> 57
     <212> DNA
     <213> Artificial Sequence
<220>
     <223> Description of Artificial Sequence:primer DNA
     <400> 75
     gtccgcctct gagtcaggaa acattttcag acctatggaa actacttcct gaaaacg
      <210> 76
      <211> 58
      <212> DNA
      <213> Artificial Sequence
      <220>
      <223> Description of Artificial Sequence:primer DNA
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gaccgttttc aggaagtagt ttccataggt ctgaaaaatg tttcctgact cagaggcg

```
<210> 77
    <211> 57
    <212> DNA
    <213> Artificial Sequence
    <220>
    <223> Description of Artificial Sequence:oligomeric DNA
    <400> 77
    gtccgcctct gagtcaggaa acattttcag acctatggaa actacttcct gaaaacg
                                                                        57
    <210> 78
    <211> 57
    <212> DNA
r state
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:oligomeric DNA
     <400> 78
     gaccgttttc aggaagtagt ttccataggt ctgaaaatgt ttcctgactc agaggcg
     <210> 79
     <211> 57
      <212> DNA
      <213> Artificial Sequence
```

```
<220>
    <223> Description of Artificial Sequence: oligomeric DNA
    <400> 79
    gtccgcctgt gagtatgcct cgttttatgg attattggga gggtcttaat gaaaacg
                                                                       57
    <210> 80
    <211> 59
    <212> DNA
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence: oligomeric DNA
<400> 80
     gaccgttttc attaagaccc tcccaataat ccataaaacg aggcatactc tcagaggcg 59
     <210> 81
     <211> 35
     <212> DNA
     <213> Artificial Sequence
     <220>
     <223> Description of Artificial Sequence:primer DNA
      <400> 81
```



```
35
cgggatcdac catgggcgat aaaattattc acctg
<210> 82
<211> 29
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence:primer DNA
<400> 82
                                                                    29
ctcgacgcta acctggccta dggaattcc
<210> 83
<211> 6
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: peptide, amin
      acid residues 18-23 of human p53
<400> 83
Thr Phe Ser Asp Leu Trp
                   5
  1
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